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Synthesis of Renewable Fine-Chemical Building Blocks by Reductive Coupling between Furfural Derivatives and Terpenes

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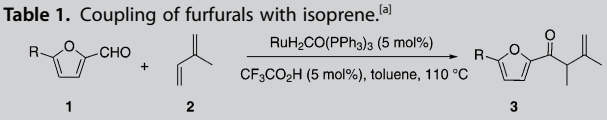
A new chemical industry, in which renewable resources such as lignocellulose or its constituents cellulose, lignin, and hemicellulose are the new raw materials, is slowly emerging. These raw materials can be transformed into a number of platform chemicals, such as 2-furfural,[1] 5-hydroxymethyl-2-furfural,[2] levulinic acid,[3] succinic acid,[4] and a host of other compounds.[5] These are the new bulk chemicals. Whereas most research in this emerging field concentrates on the conversion of biomass into platform chemicals and their conversion into monomers for polymers, very few researchers have taken the next step towards fine chemicals. Obviously, making larger, higher functionalized molecules from these C_2 to C_6 platform chemicals entails the use of C–C bond-forming reactions. In order to extend the low-carbon-footprint chemistry that is connected with biomass conversion it is important to focus on catalyzed C–C bond forming reactions that avoid the use of stoichiometric leaving groups.

Chemistry developed by Krische and co-workers using reductive coupling of alkenes, dienes, and alkynes to electrophiles undeniably matches this important criterion.[6] This methodology is by now well-developed and has a wide scope. A range of coupling reactions between aldehydes or primary alcohols and different unsaturated compounds such as dienes,[7] allenes,[8] allyl acetate,[9] and many other substrates[10] using a metal catalyst and without the use of stoichiometric reagents has been described. Many other researchers have now contributed to this important field.[11] We only found one example where this type of chemistry is applied to furfural.[12]

Furfural is readily obtainable by treatment of C_5 sugars with acids at elevated temperatures.[1d] In practice, it is often made from agricultural waste such as oat hulls, which contain C_5-sugar-rich hemicellulose. Its worldwide production volume is already in excess of 400 000 t a^{-1}. Furfural has a range of applications. To build a new product tree based on this readily available platform chemical, we evaluated its reductive coupling to renewable terpenes. Thus, we report herein the coupling of 5-substituted furfurals with isoprene[13] and myrcene,[14] using the conditions developed by Krische et al.

In a first example furfural (**1a**) was coupled with isoprene **2** to form β,γ-unsaturated ketone **3a** in good yield (Table 1, entry 1). The catalyst used is the ruthenium dihydride complex

Table 1. Coupling of furfurals with isoprene.[a]



1 2 3

Entry	R	Product	Yield[b]
1	R = H, **1a**	**3a**	76%
2	R = Me, **1b**	**3b**	91%
3	R = Br, **1c**	**3c**	85%
4	R = Ph, **1d**	**3d**	90%

[a] Reaction conditions: $RuH_2(CO)(PPh_3)_3$ (5 mol%), toluene (0.3 mL), trifluoroacetic acid (5 mol%), aldehyde (0.6 mmol), isoprene (3 mmol), 110 °C, 18 h. [b] Isolated yields.

$RuH_2(CO)(PPh_3)_3$, which is activated by the use of trifluoroacetic acid. To probe the scope of this reaction, three different 5-substituted furfurals were tested: 5-methylfurfural (**1b**), 5-bromofurfural (**1c**), and 5-phenylfurfural (**1d**). These three substrates were chosen because they are commercially available and also to investigate the influence of substituents on the reaction. All reactions gave full conversion to the desired product after 18 h and no side-products were detected. Products **3b** and **3d** (entries 2 and 4) were isolated in very good yields (≥90%). The halogen-substituted product **3c** (entry 3) was obtained in lower yield than the aliphatic and aromatic substituents. The fact that furfural itself (entry 1) gave only 76% yield whilst full conversion was observed and no side-product was detected might stem from its decarbonylation, leading to CO and furan. This decarbonylation phenomenon has been described before with ruthenium–hydride catalysts in hydroacylation reactions.[15]

Table 2 shows the coupling of furfural and 5-substituted furfurals with myrcene **4**, using the same conditions. In the case of **5a** (entry 1), full conversion was reached after 18 h and no side-product was detected. The product of the coupling to the diene part of myrcene was obtained in very good yields. On the contrary, in the case of **5b**, **5c**, and **5d** (entries 2, 3, and 4), the crude ^{1}H NMR spectrum shows full conversion of the starting material to two different products. The major one is the desired product and the minor one (5 to 10%, based on

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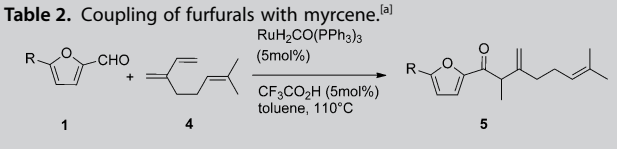
Table 2. Coupling of furfurals with myrcene.[a]



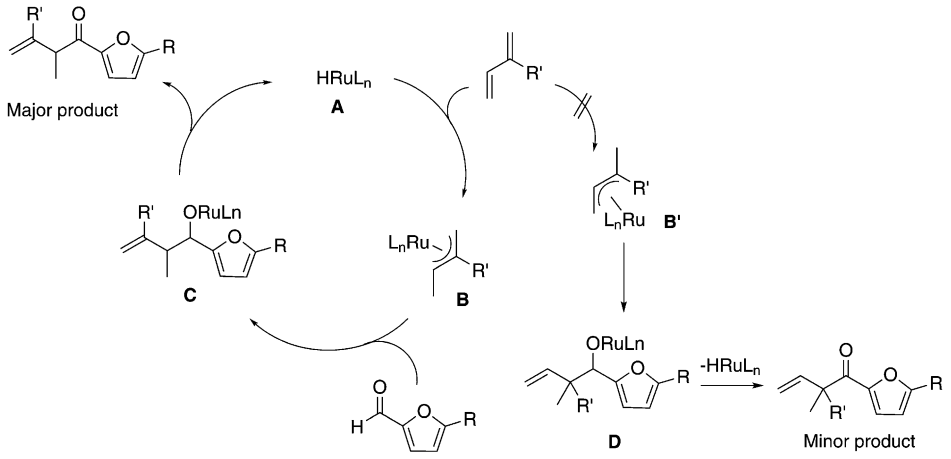
1 4 5

Entry	R	Product	Yield[b]
1	R = H, **1a**	**5a**	88%
2	R = Me, **1b**	**5b**	95%
3	R = Br, **1c**	**5c**	78%
4	R = Ph, **1d**	**5d**	94%

[a] Reaction conditions: $RuH_2(CO)(PPh_3)_3$ (5 mol%), toluene (0.3 mL), trifluoroacetic acid (5 mol%), aldehyde (0.6 mmol), myrcene (3 mmol), 110 °C, 18 h. [b] Isolated yields.

^{1}H NMR) is another isomer of the product, with a quaternary center (vide infra). Despite the presence of a side-product in these reactions, **5b** and **5d** were isolated in yields in excess of 90%, and **5c** in 78% yield. The presence of the halogen group on the furan ring leads to a lower yield.

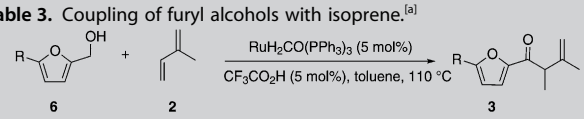
The mechanism of this reaction was established by Krische et al.[7] and Ryu et al.[12] It was confirmed using ^{1}H NMR by Ryu et al., whereas Krische et al. used deuteration experiments. The reaction proceeds via insertion of the least-hindered alkene into the ruthenium–hydride bond of **A**, leading to a ruthenium π-allyl species **B** (Scheme 1). Reaction thereof with the aldehyde, to give **C**, is followed by beta-hydride elimination, which delivers the ketone. When using aromatic aldehydes or alcohols as the substrate, only this isomer is observed. However, in reactions with formaldehyde, the product with the quaternary center is formed. Krische et al. assumed that this takes place via the minor allyl complex **B′**, the formation of which is sterically disfavored.[7c] However, the chairlike transition state that is formed during reaction of **B′** with formaldehyde (not shown in Scheme 1) is lower in energy than the one based on **B**. With other aldehydes, this is not the case.



Scheme 1. Proposed catalytic cycle.

Reacting primary alcohols with the diene is also possible; presumably, the reaction is initiated by a dehydrogenation of the alcohol to the aldehyde.[7] Although the alcohol resulting from insertion of the aldehyde in the ruthenium allyl complex would be the expected product in this reaction, in practice mixtures of the alcohol and the ketone are formed. Krische et al. have shown that it is possible to steer the reaction fully towards the ketone in the absence of added ligand; a situation that promotes beta-hydride elimination. This is the method we have used here (Table 3). Whether the hydrogen eliminated in the dehydrogenation ends up as hydrogen or if it reduces the diene is unclear. Unfortunately, the corresponding alcohol of **1c** was not stable, so no reaction using this substrate could be performed. Furylalcohol **6** and derivatives were coupled to isoprene using the same conditions as above. These reactions showed very good selectivity as no side-product was detected (Table 3), and all three products were isolated in high yields.

Table 3. Coupling of furyl alcohols with isoprene.[a]



6 2 3

Entry	R	Product	Yield[b]
1	R = H, **6a**	**3a**	82%
2	R = Me, **6b**	**3b**	88%
3	R = Ph, **6d**	**3d**	85%

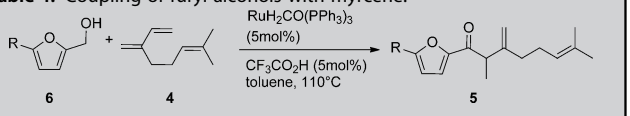
[a] Reaction conditions: $RuH_2(CO)(PPh_3)_3$ (5 mol%), toluene (0.3 mL), trifluoroacetic acid (5 mol%), alcohol (0.6 mmol), isoprene (3 mmol), 110 °C, 18 h. [b] Isolated yields.

Table 4 shows the coupling of the corresponding alcohols to myrcene. Again, very good yields were obtained and in the case of **5b** and **5d**, the presence of the minor isomer was detected in small amounts (ca. 5%, by ^{1}H NMR).

Lastly, HMF (**7**), which bears both an aldehyde and an alcohol function, was reacted with isoprene (Scheme 2). The double coupling product was isolated in 48% yield.

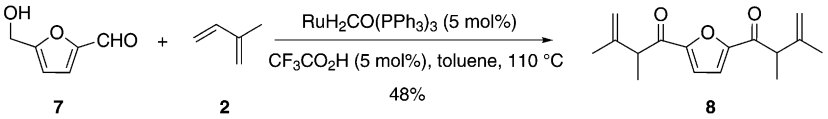
After having established a high-yielding synthesis of the ketone coupling products, we decided to reinvestigate the reaction with the alcohols with the aim of obtaining the alcohol product. We expected to obtain the alcohol in good yields using an excess of ligand, which suppresses beta-hydride elimination of the formed ruthenium alkoxide. To study the formation of the alcohol, the reaction between furyl alcohol **6a** and isoprene was chosen as the model reaction. We again used the conditions described by Krische et al.: $RuHCl(CO)(PPh_3)_3$ in combination with (*R*)-BINAP and *m*-nitro-benzoic acid. This

Table 4. Coupling of furyl alcohols with myrcene.[a]



Entry	R	Product	Yield[b]
1	R = H, **6a**	**5a**	88%
2	R = Me, **6b**	**5b**	93%
3	R = Ph, **6d**	**5d**	91%

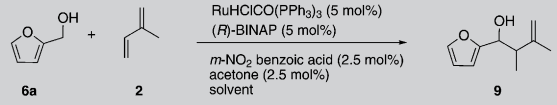
[a] Reaction conditions: $RuH_2(CO)(PPh_3)_3$ (5 mol%), toluene (0.3 mL), trifluoroacetic acid (5 mol%), alcohol (0.6 mmol), myrcene (3 mmol), 110 °C, 18 h. [b] Isolated yields.



Scheme 2. Coupling of HMF to isoprene

proved to be a better catalyst for this reaction than the ruthenium dihydride (73% isolated yield, instead of 27% for the dihydride catalyst). Several solvents were tried (Table 5), and toluene was the solvent that gave the best conversion (more than 95% based on ^{1}H NMR). Unfortunately the corresponding ketone was always obtained as a byproduct and the yield of the alcohol never exceeded 73%. The reaction was also carried out at higher temperatures (100 and 110 °C, entries 5 and 6), but this led to a further increase of the formation of the ketone.

Table 5. Coupling of furyl alcohols with isoprene to the corresponding alcohol.[a]



Entry	Solvent	*T* [°C]	Yield[b]
1	THF	95	58% (53%)
2	DMF	95	38% (35%)
3	1,4-dioxane	95	36% (33%)
4	toluene	95	77% (73%)
5	toluene	100	69% (64%)
6	toluene	110	63% (60%)

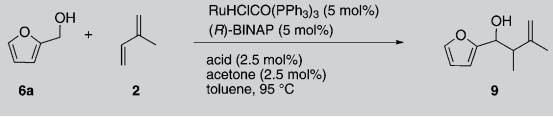
[a] Reaction conditions: $RuHCl(CO)(PPh_3)_3$ (5 mol%), toluene (0.3 mL), (*R*)-BINAP (5 mol%), *m*-NO_2 benzoic acid (2.5 mol%), acetone (2.5 mol%), furyl alcohol (0.6 mmol), isoprene (3 mmol), 95 °C, 18 h. [b] ^{1}H NMR yields (isolated yields in parentheses).

The effect of the acid additive was then studied (Table 6). Different acids were screened, but none of them really improved the yield of alcohol **9**. Use of acetic acid (entry 1) and *p*-methoxybenzoic acid (entry 4) gave the product in a yield of 79%, which is comparable to the 77% yield obtained using *m*-nitrobenzoic acid. There is no clear correlation between the pK_a of the acid and the yield of **9**. For example, use of *p*-methoxybenzoic acid (pK_a = 4.5) led to a similar yield as use of *m*-nitrobenzoic acid (pK_a = 3.4), while the use of *m*-methoxybenzoic acid, which also has a pK_a of 4.5 (entry 5) led to a much lower yield of 30%. Use of a much stronger acid (benzenesulfonic acid, pK_a = −6.5, entry 2) gave a relatively good yield of 72%.

Because the ruthenium complex we use is a known transfer-hydrogenation catalyst, a hydrogen donor (2-propanol) was added to the reaction mixture in order to convert the ketone (**3a**) back to the alcohol (Table 7). Different amounts (0.5, 1, and 2 equiv relative to the substrate) of 2-propanol were used, but this resulted in a lower conversion of the starting material, possibly because 2-propanol is competing with the substrate.

Because the addition of a hydrogen donor did not improve the yield, different ligands were screened in the reaction to see if the selectivity towards the alcohol could be further improved (Table 8). The use of BIPHEP or (*R*)-Tol-BINAP (entries 4 and 5) resulted in a lower conversion but the selectivity towards the alcohol was improved, whereas

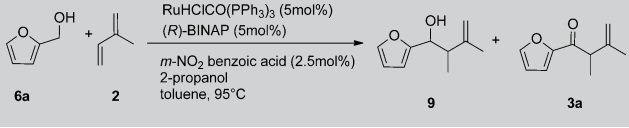
Table 6. Effect of the acid.[a]



Entry	Acid	Conversion[b]	Yield of **9**[c]
1	acetic acid	92%	79%
2	benzenesulfonic acid	95%	72%
3	benzoic acid	57%	45%
4	*p*-MeO-benzoic acid	94%	79%
5	*m*-MeO-benzoic acid	38%	30%
6	*p*-NO_2-benzoic acid	80%	67%

[a] Reaction conditions: $RuHCl(CO)(PPh_3)_3$ (5 mol%), Toluene (0.3 mL), (*R*)-BINAP (5 mol%), acid (2.5 mol%), acetone (2.5 mol%), furyl alcohol (0.6 mmol), isoprene (3 mmol), 95 °C, 18 h. [b] Conversions calculated by ^{1}H NMR. [c] ^{1}H NMR yields.

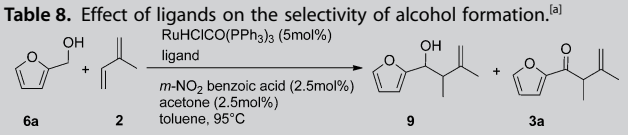
Table 7. Effect of 2-propanol.[a]



Entry	Equiv 2-propanol	Conv.[b]	Yield of **9**[c]	Yield of **3a**[c]
1	0.5	80%	67%	10%
2	1	57%	50%	5%
3	2	45%	38%	4%

[a] Reaction conditions: $RuHCl(CO)(PPh_3)_3$ (5 mol%), Toluene (0.3 mL), (*R*)-BINAP (5 mol%), *m*-NO_2 benzoic acid (2.5 mol%), 2-propanol (0.3, 0.6 or 1.2 mmol), furyl alcohol (0.6 mmol), isoprene (3 mmol), 95 °C, 18 h. [b] Conversions calculated by ^{1}H NMR. [c] ^{1}H NMR yields.

Table 8. Effect of ligands on the selectivity of alcohol formation.[a]



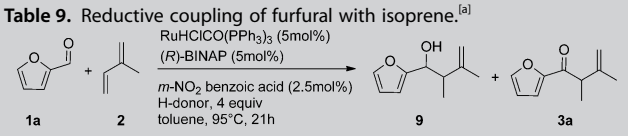
Entry	Ligand	Equiv	Conv.[b]	Yield of **9**[c]	Yield of **3a**[c]
1	(*R*)-BINAP	1	≥95%	77%	19%
2	(*R*)-BINAP	2	86%	72%	14%
3	(p-MeOC$_6$H$_4$)$_3$P	3	73%	53%	20%
4	BIPHEP[d]	1	48%	46%	2%
5	(*R*)-Tol-BINAP[e]	1	30%	27%	3%

[a] Reaction conditions: RuHCl(CO)(PPh$_3$)$_3$ (5 mol%), Toluene (0.3 mL), ligand, m-NO$_2$-benzoic acid (2.5 mol%), acetone (2.5 mol%), furyl alcohol (0.6 mmol), isoprene (3 mmol), 95 °C, 18 h. [b] Conversions calculated by ^{1}H NMR. [c] ^{1}H NMR yield. [d] BIPHEP = 2,2′-bis(diphenylphosphino)-1,1′-biphenyl. [e] (*R*)-Tol-BINAP = (*R*)-(+)-2,2′-bis(di-*p*-tolylphosphino)-1,1′-binaphthyl.

use of a monodentate phosphine (entry 3) resulted in an increase of the ketone byproduct. Two equivalents of (*R*)-BINAP instead of one (entry 1) were also used in the reaction, but this led to very similar results (72% yield).

Finally, aldehyde **1a** was tested as a starting material for the formation of alcohol **9** in the presence of 2-propanol or formic acid as hydrogen donor (Table 9). In all cases the reaction did not go to completion and the amount of ketone obtained remained high (between 20 and 30%).

Table 9. Reductive coupling of furfural with isoprene.[a]



Entry	Solvent	H-donor	Conv.[b]	Yield of **9**[c]	Yield of **3a**[c]
1	THF	2-propanol	40%	18%	22%
2	THF	HCOOH	45%	26%	19%
3	toluene	2-propanol	64%	44%	20%
4	toluene	HCOOH	91%	60%	31%

[a] Reaction conditions: RuHCl(CO)(PPh$_3$)$_3$ (5 mol%), Toluene (0.3 mL), (*R*)-BINAP (5 mol%), m-NO$_2$ benzoic acid (2.5 mol%), H-donor (4 equiv), furyl alcohol (0.6 mmol), isoprene (3 mmol), 95 °C, 18 h. [b] Conversions calculated by ^{1}H NMR. [c] ^{1}H NMR yields.

In conclusion, we report the synthesis of new multifunctional building blocks from renewable resources: furfural, isoprene, and myrcene. The β,γ-unsaturated alcohol obtained by reacting furfural with isoprene with a modified catalyst was obtained in 73% isolated yield, with the remainder being the ketone. The β,γ-unsaturated ketones that were obtained in high isolated yields are potentially interesting building blocks because they possess several positions amenable to further functionalization. Furthermore, this reaction is attractive because it offers an atom economy of 100% and uses readily available substrates while avoiding the use of stoichiometric organometallic reagents.

Experimental Section

General procedure for the preparation of adducts: To a flame-dried sealable Schlenk flask were added RuH$_2$(CO)PPh$_3$ (27 mg, 0.03 mmol), toluene (0.3 mL), trifluoroacetic acid (3.4 mg, 0.03 mmol), the aldehyde (0.6 mmol) or the alcohol (0.6 mmol), and the freshly distilled diene (3 mmol). The Schlenk tube was closed and the reaction mixture was heated at 110 °C for 18 h. The reaction mixture was concentrated in vacuo and purified by flash column chromatography.

General procedure for the preparation of **9**: To a flame-dried Schlenk flask were added RuHCl(CO)PPh$_3$ (28 mg, 0.03 mmol), toluene (0.3 mL), (*R*)-BINAP (19 mg, 0.03 mmol), m-NO$_2$ benzoic acid (2.5 mg, 0.015 mmol), acetone (0.87 mg, 0.015 mmol), furyl alcohol (58 mg, 0.6 mmol), and freshly distilled isoprene (205 mg, 3 mmol). The Schlenk tube was closed and the reaction mixture was heated at 95 °C for 18 h. The reaction mixture was concentrated in vacuo and purified by flash column chromatography to furnish the corresponding product **9**.

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Keywords: biomass · heterocycles · reductive couplings · ruthenium · terpenoids

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